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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Our Ref.: 1038-517 MIS:as

#13
MRJ
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In re

Application No.: 08/501,743

Applicant: Raafat E.F. Fahim et al

Title: ACELLULAR PERTUSSIS VACCINES AND METHODS OF PREPARATION THEREOF

Filed: July 12, 1995

Group No.: 1645

Examiner: A. Caputa

May 12, 1999

APPEAL BRIEF AND REQUEST FOR EXTENSION OF TIME

BY COURIER

The Commissioner of Patents
and Trademarks
BOX AF,
Washington, D.C.
20231, U.S.A.

Dear Sir:

1. Introduction

This Appeal Brief is submitted pursuant to applicant's appeal from a Final Rejection of claims 27 to 39 and 42. The enclosed cheque includes the prescribed fee. Three copies of the Appeal Brief are provided herewith.

2. Extension of Time

Petition is hereby made under the provisions of 37 CFR 1.136(a) for an extension of four months of the period for filing this Appeal Brief. The enclosed cheque includes the prescribed fee.

3. Real Party of Interest

The real party of interest with respect to this patent application is Connaught Laboratories Limited by virtue of Assignments from the inventors to Connaught Laboratories Limited recorded at Reel 7777/0660; 7777/0666; and 7777/0657 on January 24, 1996.

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4. Related Appeals and Interferences

The appellants, the appellants' legal representatives and assignee, are unaware of any pending appeals or interferences which will directly affect or be affected by or have a bearing on the Board's decision in the pending appeal.

5. Status of Claims

This application was filed with claims 1 to 42. In response to a restriction requirement, applicants elected claims 27 to 42 for examination. The Examiner withdrew claims 1 to 26 from consideration. These claims along with claims 40 and 41 were deleted from this application. Claims 27 to 39 and 42 are pending and are on appeal. A copy of the appealed claims appears in an Appendix hereto.

6. Issues

The following issues are presented for consideration on this appeal:

(a) Rejection of claims 27 to 39 under 35 USC 112, second paragraph, as being indefinite;

(b) Rejection of claims 27 to 29, 31 to 34, 38, 39 and 42 under 35 USC 102(b) as being anticipated by Englund et al; and

(c) Rejection of claims 27 to 39 and 42 under 35 USC 103(a) as being unpatentable over Englund et al.

7. Status of Amendments

An Amendment after Final Action has been submitted at the same time as this Appeal Brief to amend claim 27 to obviate the rejection of the claim under 35 USC 112, second paragraph. No Advisory Action has been received with respect to such Amendment.

8. Summary of Invention

This invention relates to a vaccine composition for the prevention of disease caused by *Bordetella pertussis*. The vaccine composition is specifically for protecting an at-risk human population and comprises:

- pertussis toxoid
- filamentous haemagglutinin
- pertussis
- agglutinogens

of *B. pertussis*, all in purified form. The components are formulated in selective relative amounts such as to confer protection to the extent of at least about 70% of members of the at-risk population.

9. Grouping of Claims

As discussed in more detail below, all claims do not stand or fall together, but rather each claim is individually patentable.

10. Argument

(a) Background to the Invention

Whooping cough or pertussis is a severe, highly contagious upper respiratory tract infection caused by *Bordetella pertussis*. The World Health Organization estimates that there are 60 million cases of pertussis per year and 0.5 to 1 million associated deaths. In unvaccinated populations, a pertussis incidence rate as high as 80% has been observed in children under 5 years old. Although pertussis is generally considered to be a childhood disease, there is increasing evidence of clinical and asymptomatic disease in adolescents and adults.

The introduction of whole-cell vaccines composed of chemically- and heat-inactivated *B. pertussis* organisms in the 1940's was responsible for a dramatic reduction in the incidence of whooping cough caused by *B. pertussis*. The efficacy rates for whole-cell vaccines have been estimated at up to 95% depending on case definition. While infection with *B. pertussis* confers life-long immunity, there is increasing evidence for waning protection after immunization with whole-cell vaccines. Several reports citing a relationship between whole-cell pertussis vaccination, reactogenicity and serious side-effects led to a decline in vaccine acceptance and consequent renewed epidemics. More recently defined component pertussis vaccines have been developed.

The first acellular vaccine developed was the two-component PT + FHA vaccine (JNIH 6) of Sato et al. This vaccine was prepared by co-purification of PT and FHA antigens from the culture supernatant of *B. pertussis* strain Tohama, followed by formalin toxoiding. Acellular vaccines from various manufacturers and of various compositions have been used successfully to immunize Japanese children against whopping cough since 1981 resulting in a dramatic decrease in incidence of disease. The JNIH 6 vaccine and a mono-component PT toxoid vaccine (JNIH 7) were tested in a large clinical trial in Sweden in 1986. Initial results indicated lower efficacy than the

reported efficacy of a whole-cell vaccine, but follow-up studies have shown it to be more effective against milder disease diagnosed by serological methods. However, there was evidence for reversion to toxicity of formalin-inactivated PT in these vaccines. These vaccines were also found to protect against disease rather than infection.

Various acellular pertussis vaccines against whooping cough have been developed and include various *B. pertussis* antigens, including pertussis toxin (PT), filamentous haemagglutinin (FHA), the 69 kDa outer membrane population (pertactin) and fimbrial agglutinogens. These compositions are identified in Table 1 of the text, appearing on page 45 of the specification. Several techniques of chemical detoxication have been used for PT, including inactivation with formalin, glutaraldehyde, hydrogen peroxide, and tetranitromethane.

Thus, current commercially-available acellular pertussis vaccines may not contain appropriate formulations of appropriate antigens in appropriate immunogenic forms to achieve a desired level of efficacy in a pertussis-susceptible human population.

(b) The Present Invention

The present invention is based on the results of a multi-centre, double-randomized, placebo-controlled efficacy trial in 10,000 infants held in Sweden, a country where there is no routine vaccination against whooping cough and hence there is a large at-risk population and a high incidence of whooping cough.

The trial, described on page 41 to 43 of the specification, was conducted using:

(a) A two-component vaccine containing PT (25 μg) and FHA (25 μg) and also diphtheria toxoid (D) (17 Lf) and tetanus toxoid (T) (10 Lf). The latter two components are often formulated with pertussis vaccines in a single dose, DTP vaccine.

(b) A five-component vaccine containing PT (10 μg), FHA (5 μg), fimbrial agglutinogens 2 and 3 (5 μg) and pertactin (3 μg) along with D (25 Lf) and T (5 Lf). The composition was formulated with 1.5 μg of aluminum phosphate as adjuvant and 0.6% 2-phenoxyethanol as preservative.

(c) A U.S. Licensed commercially-available whole-cell based DTP vaccine.

The results of the trial are given in Table 4, from which it can be seen that the five-component vaccine, depending on the case definition of infection, had an efficacy greater than 70%, and was superior to the two-component acellular vaccine and the whole-cell based vaccine.

Prior to this trial, the contribution of the various *B. pertussis* components in pertussis vaccines in selected relative amounts to the efficacy of such vaccines was unknown and could not have been known without the actual results of the trial. The results of the trial show the superiority of the composition containing PT, FHA, pertactin and agglutinogens to one containing only PT and FHA and a whole cell based vaccine.

The applicants claimed invention resides in providing a vaccine composition for protecting an at-risk population from infection by *B. pertussis* and comprising purified PT, FHA, pertactin and agglutinogens which protects to an extent of at least about 70%, preferably at least about 80% for a case of pertussis having a spasmodic cough of duration at least 21 days and confirmed bacterial infection (claim 31) and at least about 70% for a case of mild pertussis having a cough of at least one day duration (claim 32), of the at-risk population. The applicants have determined a hitherto unknown and unexpected result.

(c) Rejection of Claims 27 to 39 under 35 USC 112, second paragraph

The Examiner rejected claims 27 to 39 under 35 USC 112, second paragraph, as being indefinite in the use of the phrase "a case of disease caused by infection by *B. pertussis*". In the first Office Action, the Examiner stated:

> "The art recognizes B. pertussis as the causative agent of pertussis, but does not recognize this organism to be the causative agent of other diseases. Therefore it is unclear whether the claimed vaccine compositions are intended to protect against only pertussis or whether unspecified diseases are intended."

and repeated the argument in the Final Action.

The applicants fail to see the indefiniteness. Claim 27 quite clearly recites that the vaccine composition is for protecting against disease caused by infection by *B. pertussis*. This phraseology clearly refers to the disease condition (whooping cough) which is caused by *B. pertussis* and hence the composition is intended to protect only against whooping cough. In any event, it is not seen how a

composition formulated from antigens of one bacterium might be expected to provide protection against a quite different bacterium.

In any event, it is proposed to amend claim 27 to specify "the" disease caused by infection by *B. pertussis* and to specify that the disease is whooping cough. While it is believed that claim 27 is clear in scope with respect to the language employed, nevertheless the language change is proposed to meet the Examiner's concern.

For the above reasons, it is submitted that the Examiner is in error and claim 27 is clear in scope and that claims 27 to 39 are not open to rejection under 35 USC 112, second paragraph.

(d) Rejection of Claims 27 to 29, 31 to 34, 38, 39 and 42 under 35 USC 102(b)

This rejection is based on the disclosure of Englund et al. While the Englund et al reference describes a five-component acellular pertussis composition which is formulated according to claim 29 in respect of the individual pertussis components, there is no indication that such formulation may be used to achieve an efficacy level of at least about 70% in an at-risk population. Indeed, as stated on page 1436, right-hand column:

> "... this vaccine now is being studied in the NIAID-sponsored Swedish Efficacy Trial, which began in March 1992."

Thus, the surprising result achieved in the Swedish Efficacy Trial and on which the present invention is based was unknown at the time of the publication of the Englund et al reference and would not be known until the trial was complete and the results analyzed. There could be no prediction from the information contained in Englund et al that the result achieved could be achieved or was achievable.

The Examiner appears to acknowledge that such is the case, stating in the Final Action:

> "... the vaccine of the prior art appears to be the same as the vaccine claimed by applicants. Accordingly, the vaccine as set forth by Englund et al appears to be consistent with various characteristics inherent to the vaccine as claimed (i.e., vaccine would have an efficacy of at least about 70% as specified in claim 27)." (emphasis added)

While the Englund et al reference may describe a composition having the same components as applicant's composition, nevertheless, it is submitted that the

absence of any manner of predicting the efficacy of such a composition in the absence of a large scale clinical trial among an at-risk population distinguishes the invention over the prior art. While the trials reported in Englund et al noted pertussis-specific antibody responses, as is well known, the eliciting of an antibody response is not necessarily predictive of protection. It is only by conducting the clinical trial described in the application that it is possible to establish whether or not a protective immune response can be achieved and the level to which an at-risk population can be protected.

In view of this unpredictability, it follows that the cited prior art lacks a basic teaching, such as would lead to a determination of anticipation. Anticipation requires that every feature of the claimed subject matter be found in the cited prior art. The cited prior art lacks the feature of applicants claims that the individually purified antigens are formulated to provide an extent of protection of at least about 70% against a case of disease caused by infection by *B. pertussis* in an at-risk population.

In the absence of such a teaching in the art and in the absence of means to predict such a teaching, it is submitted that the Englund et al reference falls short of being an anticipatory reference. It is submitted it is not a question of showing that the compositions of the prior art do not posses the same functional characteristics as the composition claimed, as suggested by the Examiner in the Final Action, but rather that the prior art cannot predict the feature which distinguishes the composition over the prior art.

Claim 27 generically defines the composition of the invention, while claim 42 defines a method of immunizing an at risk population by employing an immunoeffective amount of the composition of claim 27. Claim 28 defines ranges of amounts of the individual pertussis antigens present in a single human dose of the composition. Claim 29 defines a specific combination of components.

Claims 31, 32 and 33 define further specific definitions of the extent of protection. As in the case of claim 27, these specific effects:

- the extent of protection is at least about 80% for a case of pertussis having a spasmodic cough of duration at least 21 days and confirmed bacterial infection (claim 31)

- the extent of protection is at least about 70% for a case of mild pertussis having a cough of at least one duration (claim 32)

- for the composition of claim 28, the extent of protection is about 85% for a case of spasmodic cough of duration at least 21days and confirmed bacterial infection (claim 33)

are not disclosed in the cited prior art and are not predictable therefrom. These claims, therefore, also are patentable over the applied art.

Claim 34 defines the form of the agglutinogens of claim 27, namely Agg 2 and Agg 3 substantially free from Agg 1. While the Englund et al reference describe agglutinogens in this form, the reference is defective with respect to disclosure of the level of efficacy.

Claim 38 recites that the composition of claim 27 further comprises an adjuvant which, according to claim 39, may be alum. As in the case of claim 34, while Englund et al describes formulation with alum as an adjuvant, nevertheless, the reference is defective with respect to disclosure of the level of efficacy.

Accordingly, it is submitted that the Examiner is in error and that claims 27 to 29, 31 to 34, 38, 39 and 42 are not anticipated by Englund et al and hence not open to rejection under 35 USC 102(b).

(d) Rejection of Claims 27 to 39 and 42 under 35 USC 103(a)

The Examiner has relied on Englund et al as a reference. The deficiencies of Englund et al as a reference have been discussed above. Of the claims not rejected as anticipated, the following observations can be made:

- claim 30 defines an alternative specific composition according to claim 28.
- claim 35 recites a specific weight ratio of Agg 2:Agg 3 of about 1.5:1 to about 2:1, not disclosed or suggested by Englund et al.
- claim 36 recites the additional presence of tetanus toxoid and diphtheria toxoid in the vaccine composition of claim 27 while claim 37 recites specific proportions of these components per human dose. While, as noted earlier, it is conventional to formulate pertussis components with tetanus toxoid and diphtheria toxoid, nevertheless, the specific amounts specified in claim 37 are neither disclosed in or suggested by the cited reference.

The Examiner states in the Final Action that:

> "The mere discovery of characterizing features of a vaccine (e.g., the efficiency of the vaccine) does not impart unobviousness to the vaccine."

However, the invention relates to an inherently unpredictable art. Applicant's contribution to this art is not "mere discovery" but rather the finding that, by formulating the composition in specific proportions, an unexpected result is achieved, namely an efficacy of at least 70% among an at-risk population, a result neither disclosed in nor suggested by the prior art, nor predictable theefrom. The observation of the generation of antibodies in otherwise healthy adults and children does not lead to the expectation that an at-risk population can be protected to the extent of at least about 70%, as required by applicants claims.

Accordingly, it is submitted that the Examiner is in error in rejecting claims 27 to 39 and 42 being unpatentable and hence the claims are not open to rejection under 35 USC 103(a).

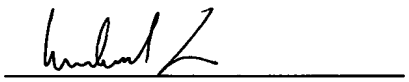
11. Summary

In summary of this Appeal Brief, it is submitted that the rejections of:

- claims 27 to 39 under 35 USC 112, second paragraph,
- claims 27 to 29, 31 to 34, 38, 39 and 42 under 35 USC 102(b),
- claims 27 to 39 under 35 USC 103(a)

should be REVERSED.

Respectfully submitted,



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APPENDIX
CLAIMS APPEALED

27. A vaccine composition for protecting an at-risk human population against a case of disease caused by infection by *B. pertussis*, which comprises pertussis toxoid, filamentous haemagglutinin, pertactin and agglutinogens of *B. pertussis* in purified form in selected relative amounts to confer protection to the extent of at least about 70% of members of the at-risk population.

28. The vaccine of claim 27 wherein said pertussis toxoid is present in an amount of about 5 to about 30 μg nitrogen, said filamentous haemagglutinin is present in an amount of about 5 to about 30 μg nitrogen, said pertactin is present in an amount of about 3 to about 15 μg nitrogen and said agglutinogens are present in an amount of about 1 to about 10 μg nitrogen, in a single human dose.

29. The vaccine of claim 28 containing about 10 μg nitrogen of pertussis toxoid, about 5 μg nitrogen of filamentous haemagglutinin, about 5 μg nitrogen of pertactin and about 3 μg nitrogen of agglutinogens in a single human dose.

30. The vaccine of claim 28 containing about 20 μg nitrogen of pertussis toxoid, about 20 μg nitrogen of filamentous haemagglutinin, about 5 μg nitrogen of pertactin and about 3 μg nitrogen of agglutinogens in a single human dose.

31. The vaccine of claim 27 wherein the extent of protection is at least about 80% for a case of pertussis having a spasmodic cough of duration at least 21 days and confirmed bacterial infection.

32. The vaccine of claim 27 wherein the extent of protection is at least about 70% for a case of mild pertussis having a cough of at least one day duration.

33. The vaccine of claim 28 wherein the extent of protection is about 85% for a case having a spasmodic cough of duration at least 21 days and confirmed bacterial infection.

34. The vaccine of claim 27 wherein said agglutinogen comprise fimbrial agglutinogen 2 (Agg 2) and fimbrial agglutinogen 3 (Agg 3) substantially free from agglutinogen 1.

35. The vaccine of claim 34 wherein the weight ratio of Agg 2 to Agg 3 is from about 1.5:1 to about 2:1.

36. The vaccine of claim 27 further comprising tetanus toxoid and diphtheria toxoid.

37. The vaccine of claim 36 wherein said diphtheria toxoid is present in an amount of about 15 Lfs and tetanus toxoid is present in an amount of about 5 Lfs.

38. The vaccine of claim 27 further comprising an adjuvant.

39. The vaccine of claim 38 wherein the adjuvant is alum.

42. A method of immunizing an at-risk human population against disease caused by infection by *B. pertussis*, which comprises administering to members of the at-risk human population an immunoeffective amount of the vaccine composition of claim 27 to confer protection to the extent of at least about 70% of the members of the at-risk population.